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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/468,002	12/20/99	NEGULESCU	P AUR01130-2

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1647	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/468,002	NEGULESCU ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Formal Matters

A. Amendment B, filed 3/7/00, has been entered into the record.

B. Claims 1-62 were pending in the application. Claims 1-62 have been canceled and new claims 63-109 have been added. Therefore, claims 63-109 are pending.

2. Information Disclosure Statement

A. U.S. Patent No. 5,741,657 has been lined through since it appears twice on the Form PTO-1449.

B. The Hidenori et al. reference has been lined through since Hidenori is not the author of this reference.

3. Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 63-109 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying GPCRs or ligands by using the Gα15 of SEQ ID NO:2, does not reasonably provide enablement for a method of identifying a GPCR by using all Gα15 G proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence

of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claim is excessive with regard to claiming all methods of identifying GPCRs and ligands by using all Gα15 G proteins. The Gα15 proteins are a subfamily of G proteins which have one or more amino acid substitutions, deletions, insertions and/or additions to that encoded by SEQ ID NO:2. Applicants provide no guidance or working examples of the claimed methods using *all* G protein-coupled receptors. Furthermore, it is not predictable to one of ordinary skill in the art what constitutes a Gα15 protein, since this is only an arbitrary name given to a protein and is not identified by a unique sequence.

In summary, the breadth of the claims is extensive with regard to the claimed methods using all Gα15 proteins. There is also a lack of guidance and working examples for these Gα15 protein. These factors, along with the lack of predictability to one of ordinary skill in the art as to what constitutes a Gα15 protein, leads the Examiner to hold that undue experimentation is necessary to practice the invention as claimed.

4. Claim Rejections - 35 USC § 112, first paragraph – lack of written description

A. Claims 63-109 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims. The subfamily of "**Gα15**" proteins would have one or more amino acid substitutions, deletions, insertions and/or additions to SEQ ID NO:2. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Thus the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number

of structural differences between genus members is permitted. Although these types of changes are routinely done in the art, the specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the nucleic acid or protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:2 alone are insufficient to describe the genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

5. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claims 63-109 are rejected since the term "Gα15" is vague and indefinite. Gα15 is an arbitrary term used to describe a subfamily of proteins. Proteins can have more than one name or the name of the protein can change. This rejection can be overcome if Applicants amend the claims to recite the specific SEQ ID NO which Applicants are claiming as their invention.

B. Claims 63-109 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: there is no method step in any of the independent claims which demonstrates that the effect of the ligand is acting through the GPCR. In other words, there is no negative control in which cells

not expressing the GPCR of interest are tested to be sure that the test compounds and ligands have no effect on reporter gene expression in the absence of the GPCR..

C. Claims 71-79 and 89-90 are confusing since the metes and bound of "substantially" is not understood. Claims 71, 75 and 90 recite "substantially coupled." Claims 79 and 89 recite "substantially the same." Claims 72-74 and 76-78 are rejected since they depend from rejected base claims.

D. Claims 79 and 89 are confusing since it is not known what the "target protein" refers to. In other words, it is not clear what the target of this protein is.

6. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 63-65, 67, 81-83, 85, 89-96 and 98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al. (US Patent No. 5,691,188 on the PTO-1449) in view of Offermanns et al. (J. Biol. Chem. 270:15175-15180, 1995 on the PTO-1449). The claims recite a method of identifying GPCRs (coupled to Gαi) for a given ligand or ligands for a given GPCR. The method involves transfecting a cell with a promoter linked to a Gα15 protein polynucleotide, another promoter linked to a reporter gene, and a final promoter linked to a polynucleotide encoding a GPCR and detecting reporter gene expression after contacting the cell with a ligand. The method also involves the use of ionomycin or

thapsigargin to increase calcium levels in the cell as well as the use of PMA and intracellular calcium indicators.

Pausch et al. teach a method (column 8, line 59 – column 11, line 10) of identifying GPCRs for a given ligand or ligands for a given GPCR. The method involves transfecting a cell with a promoter linked to a Gα15 protein polynucleotide, another promoter linked to a reporter gene, and a final promoter linked to a polynucleotide encoding a GPCR and detecting reporter gene expression after contacting the cell with a ligand (column 3, lines 14-24). Pausch et al. do not teach the use of a promiscuous Gα15 protein, or GPCRs which couple to Gαi, or Gαs. However, Offermanns et al. do teach that receptors coupling to Gαi or Gαs can be coexpressed with the promiscuous Gα15 protein (Abstract and last line of the Introduction). It would have been obvious to one of ordinary skill in the art to have substituted the Gα15 protein of Offermanns et al. for the G protein of Pausch et al. for the purposes of identifying GPCRs and ligands of said GPCRs since the use of a promiscuous G protein, such as Gα15, would produce a less specific assay wherein the artisan could easily observe any modulation of GPCRs by ligands. One of ordinary skill in the art would have been successful in using the Gα15 protein of Offermanns et al. in the invention of Pausch et al. since transfection techniques involving polynucleotides into host cells and the use of reporter genes to observe functional activity of a protein were well-known and widely successful at the time. One of ordinary skill in the art would have been motivated to perform this substitution to allow for easier and more rapid screening of receptors and ligands for therapeutic or diagnostic purposes.

It would also have been obvious to one of ordinary skill in the art to have used the proper controls which would include performing the assay in cells which were not transfected with Gα15 to determine the effect of Gα15 in the system as well as to have used test the modulation of known ligands by unknown test compounds to determine the effects of these test compounds as possible therapeutic and/or further diagnostic tools to further characterize receptor-ligand interactions and receptor effects. Such competition assays can be seen in Pausch et al. on column 11, lines 47-59.

B. Claim 66 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al. (US Patent No. 5,691,188 on the PTO-1449) in view of Offermanns et al. (J. Biol. Chem. 270:15175-15180, 1995 on the PTO-1449), and further in view of Abe et al. (J. Biol. Chem. 268:12033-12039) This claim is rejected over Pausch et al. and Offermanns et al. as stated in paragraph A in the above rejection under 35 USC 103(a). Neither Pausch et al., nor Offermanns et al. teach taste receptors. However, Abe et al. do teach the cloning of a taste receptor and that these proteins are coupled to G proteins (Abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have substituted the invention of Abe et al. for the G protein-coupled receptor of Pausch et al. for the purpose of screening for compounds which modulate this G protein-coupled receptor. One of ordinary skill in the art would have been successful in using the DNA encoding the tast receptor of Abe et al. in the invention of Pausch et al. since transfection techniques involving polynucleotides into host cells and the use of reporter genes to observe functional activity of a protein were well-known and widely successful at the time. One of ordinary skill in the art would have been motivated to perform this substitution to allow for easier and more rapid screening of receptors and ligands for therapeutic or diagnostic purposes.

C. Claim 68-70, 86-88 and 99-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al. (US Patent No. 5,691,188 on the PTO-1449) in view of Offermanns et al. (J. Biol. Chem. 270:15175-15180, 1995 on the PTO-1449), and further in view of Negulescu et al. (PNAS 91:2873-7, 1994). These claims are rejected over Pausch et al. and Offermanns et al. as stated in paragraph A in the above rejection under 35 USC 103(a). Neither Pausch et al., nor Offermanns et al. teach the increasing calcium levels in the cell. However, Negulescu et al. do teach compounds which increase calcium levels in the cell (for example, Figure 4). It would have been obvious to one of ordinary skill in the art at the time of the invention to have substituted the invention of Negulescu et al. for the reporter construct of Pausch et al. since various reporter constructs and assay systems were well-known at the time and widely

successful and that the individual investigator would need to determine which reporter gene construct was most appropriate under the given experimental conditions. For example, if a calcium-responsive promoter were to be used, it would be obvious to the artisan to maintain a calcium level in the cell which would allow for the optimum visualization and measurement of any potential ligand-receptor interactions.

D. Claims 71-81, 84, 94 and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al. (US Patent No. 5,691,188 on the PTO-1449) in view of Offermanns et al. (J. Biol. Chem. 270:15175-15180, 1995 on the PTO-1449) and further in view of Hazlett et al. (Biochemistry 32:13575-13583, 1994). These claims are rejected over Pausch et al. and Offermanns et al. as stated in paragraph A in the above rejection under 35 USC 103(a). Neither of these references teaches the use of a dye or fluorescence to aid in the identification of ligands. However, Hazlett et al. do teach the synthesis of fluorescent 2'(3')-O-(N-methylanthraniloyl) derivatives (mant derivatives) of GTP, dGTP, and GDP and the aminocoumarin and fluorescein derivatives of GTP and GDP which were used as reporter groups (Abstract).

It would have been obvious to one of ordinary skill in the art to have used the fluorescent derivatives of Hazlett et al. in the invention of Pausch since the use of fluorescent dyes were well known at the time of the invention and would have given the investigators other options in the detection of GPCR-ligand interactions.

E. Claims 102-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al. (US Patent No. 5,691,188 on the PTO-1449) in view of Offermanns et al. (J. Biol. Chem. 270:15175-15180, 1995 on the PTO-1449) and further in view of Goddard et al. (ISLAR 1992 Proceedings, pages 392-399). These claims are rejected over Pausch et al. and Offermanns et al. as stated in paragraph A in the above rejection under 35 USC 103(a). Neither of these references teach a method of contacting a panel of cells

with a test chemical. However, Goddard et al. do teach fully automated, cell-based, high throughput drug screening methods in which stable reporter cell lines comprising luciferase have been made (Abstract) and wherein the assay uses a panel of cells (under "Development and automation of the OSI Screening Program").

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Goddard et al. to screen a large number of cells for GPCRs or ligands as taught by Pausch et al. since high-throughput screening assays were well-known in the art at the time of the invention and one would have been motivated to use the invention of Goddard et al. since it was well known to the artisan that high-throughput screening assays save both time and money by increasing the efficiency of the screening process.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
March 26, 2001

Gary L. Kunz

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